Atty. Dkt. No. 18733-1093

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Gary L. GRIFFITHS

Title: FLUORINATION OF PROTEINS AND PEPTIDES FOR F-18 POSITRON EMISSION TOMOGRAPHY

Appl. No.: 10/071,247

Filing Date: February 11, 2002

Examiner: P. N. Huynh

Art Unit: 1644

REQUEST FOR RECONSIDERATION UNDER 37 CFR §1.116

Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the Official Action dated March 11, 2003, the period for response to which has been extended to expire on July 11, 2003, by virtue of the accompanying petition and fee, applicants request that the above-identified application be reconsidered in light of the following remarks.

Claims 9-20 are pending and have been rejected. Claims 9-20 remain in the case.

Claims 9-12 and 16-20 remain rejected under the first paragraph of Section 112. The examiner still alleges that the specification only is enabling for a method for detecting a tissue in a patient by administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to one of the specific F-18 labeled peptides that are recited in claims 13-15, or a low molecular weight hapten conjugated to one of these F-18 labeled peptides, and then administering one of the specific F-18 labeled peptides recited in claims 13-15 or the hapten conjugate thereof, and detecting that F-18 labeled peptide by positron emission tomography. The examiner finds that bispecific antibodies and antibody fragments in which the other arm is specific to "*any* F-18 labeled peptide or and low molecular weight hapten conjugated to *any* F-18 labeled peptide" are not enabled.

The basis for the allegation of lack of enablement was that, other than the specific F-18 labeled peptides recited in claims 13-15, there is insufficient guidance about the structure (amino acid residues) of any of the F-18 labeled peptides. Previously, the examiner elaborates that "without the specific amino acid residues, one of skill in the art cannot even contemplate of making such antibody

that would have one arm specific for any F-18 labeled peptide and one arm would be specific for any tissue in a patient," citing Kuby *et al.* as showing that "immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide."

In their previous response, applicant emphasized that the making of antibodies to ***any*** immunogen is a straightforward and routine matter, and provided a detailed discussion, supported by references to the literature of how make antibodies. A skilled artisan readily can generate antibodies to any immunogen, and from those antibodies can prepare antibody fragments that are specific to the immunogen. Indeed, the examiner now admits that "the method of making antibodies to any immunogen appears to be straightforward." (Official Action at page 5, lines 16-17). She counters, however, that the term "'comprising' is open-ended. It expands the bispecific antibody or antibody fragment to include additional amino acids at either or both ends." While there would be no practical motivation for one of skill in the art to add amino acids at either or both ends of the antibody, neither would such addition necessarily preclude the utility of the present invention. Accordingly, the use of comprising language is appropriate in the present claims.

Furthermore, the examiner's position with respect to enablement in this case is directly at odds with the position she took on this issue in the parent application, now issued as U.S. 6,358,489. Claim 1 of the issued patent recites "A method for radiolabeling thiol-containing peptide with fluorine-18 (F-18), comprising reacting a peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate and triflate." Thus, the examiner had no concerns with a method of labelling *any* thiol-containing peptide with F-18, even though the claim encompasses peptides of many structures. Since the examiner concedes that the making of antibodies to any immunogen is straightforward, and the present specification enables a skilled artisan to make many different F-18 radiolabeled peptides, then the present claims to methods of detecting tissue using these antibodies to the radiolabeld peptides must necessarily be enabled.

Claims 9-12 and 16-20 also are rejected under the first paragraph of Section 112 as containing subject matter which was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claims 9-12 and 16-20 are original claims. As to original claims, possession may be shown in many ways. For example, possession may be shown, *inter alia*, by describing an actual reduction to practice of the claimed invention. Possession may also be shown

by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.[1]

For each claim drawn to a genus, as in claim 9, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice. A representative number of species means that the species which are adequately described are representative of the entire genus. There may be situations where one species adequately supports a genus. Furthermore, what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.[2]

In the present case, the exemplified species demonstrate possession of the genus of "F-18 labeled peptides" that is recited in claim 9. Three different species were explicitly disclosed. Moreover, the level of skill in this art is very high, and based on applicant's teaching the method of radiolabelling peptides could readily be extended those of skill in this art to any thiol-containing peptide. The technique entails reacting the thiol group with an F-18 bound labeling reagent which has a group that is reactive with thiols. Even peptides that do not originally comprise a free thiol group can be labeled in accordance with the present invention by first modifying the peptide to add a free thiol group by methods known to those skilled in the art. For example, the peptide can be thiolated with reagents such as 2-iminothiolane, or intrinsic disulfide bonds such as cysteine residues can be reduced. A combination of both modifications also can be performed, such as acylation of lysine residues with N-succinimidyl-3-(2- pyridylthio)-propionate (SPDP) followed by the controlled reduction of the appended disulfide bond. These techniques are discussed at the top of page 6.

[1] USPTO Written Description Guidelines.

[2] USPTO Written Description Guidelines.

Based on the foregoing, it is believed that all claims are in condition for allowance. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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